REMARKS

I. Status of the Claims

Claims 1-35 were originally filed in the parent application. In the preliminary amendment filed December 16, 2003, claims 1-10, 12, 13, and 16-35 were canceled, claim 36 was added, and claims 11 and 15 were amended. Thus, claims 11, 14, 15, and 36 were pending prior to the present amendment.

Upon entry of the present amendment, claims 15 and 36 are canceled. Claim 11 is amended so that it has the same scope as claim 15 prior to its cancellation. Reference to SEQ ID NO:1 is deleted from both claims 11 and 14. Claim 11 is further amended to recite the full name of Kv: voltage-gated potassium channel, which finds support on page 8, lines 18-22, of the specification. Claim 14 is also amended to replace "***an*** amino acid sequence of SEQ ID NO:17" with "***the*** amino acid sequence of SEQ ID NO:17." No new matter is introduced.

II. Amendment to the Specification

The Examiner has requested amendment to the specification so as to provide an abstract on a separate sheet, to ensure the proper use of trademarks, to delete embedded hyperlinks, and to provide updated priority information. The amendment to the specification is made in accordance with the Examiner's request and introduces no new matter.

III. Claim Objections

Claims 11, 14, and 15 were objected to for containing reference to non-elected subject matter, namely, SEQ ID NO:1. Claim 11 was also objected to for reciting the numbers (i), (ii), and (iv) without (iii). The present amendment to the claims has obviated the objections.

IV. Claim Rejections

A. 35 U.S.C. §112, Second Paragraph

Claims 11-15 were rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness. Specifically, the Examiner alleged that the term "Kv alpha subunit of Kv6.2" renders the claims vague and indefinite for not spelling out the full name of the abbreviations.

The relevant claims have been amended to recite the full name for Kv: voltage-gated potassium channel. The rejection is thus overcome.

B. 35 U.S.C. §112, First Paragraph

Written Description

Claims 11-15 were rejected under 35 U.S.C. §112, first paragraph, for alleged lack of written description. Specifically, the Examiner alleged that the specification provides inadequate description for all polypeptide monomers within the claim scope. Applicants respectfully traverse the rejection, particularly in view of the present amendment.

1. Standard for Written Description

According to the MPEP, to satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. Possession of a claimed invention may be demonstrated by description of the invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. MPEP §2163 I. Moreover, a strong presumption exists with regard to originally filed claims that an adequate written description of the claimed invention is present when the application is filed. MPEP §2163 I.A.

Case law indicates that structural features of a claimed invention are important for satisfying the written description requirement. The Federal Circuit in *Fiers v. Revel*, 25 USPQ2d 1601 (Fed. Cir. 1993), stated that an adequate written description "requires a precise definition, such as by structure, formula, chemical name, or physical properties." *Fiers*, 25 USPQ2d at 1606. The requirement for written description of a chemical genus is further set forth in *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997). As described by the Federal Circuit in *Lilly*, "[a] description of a genus of cDNAs may be achieved by means of ... a recitation of structural features common to the members of the genus ..." *Lilly*, 43 USPQ2d at 1406.

Moreover, proper description of functional features of a claimed invention can also satisfy the written description requirement. In *Enzo Biochem, Inc. v. Gen-Probe Incorporated*, 63 USPQ2d 1609 (Fed. Cir. 2002), the claimed polynucleotide sequences in the patent in question are defined based on their ability to differentially hybridize to reference polynucleotide sequences from deposited bacteria *N. gonorrhoeae* and *N. meningitidis*. The Federal Circuit held that this hybridization function-based description may, in some cases, satisfy the written description requirement because of "a complementary structural relationship" between the claimed sequences and the reference sequences. *Enzo*, 63 USPQ2d at 1616. The Federal Circuit further stated that "*Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 65 USPQ2d 1385, 1398 (Fed. Cir. 2003).

2. The Polypeptide Used in the Claimed Invention Is Defined by Its Structural and Functional Features

The present invention relates to the discovery of a subunit of a novel voltage-gated potassium channel, Kv6.2 monomer. The pending claims are directed to a polypeptide monomer comprising an alpha subunit of a heteromeric potassium channel. The polypeptide monomer is defined by structural and functional features: the claimed polypeptide monomer (1) has the ability to form, with at least one additional Kv alpha subunit, a heteromeric potassium channel having the characteristic of voltage gating; and (2) has an amino acid sequence that has greater than 90% amino acid sequence identity to SEQ ID NO:17. These structural and functional features can be readily determined by a person of skill in the art. It is Applicants' intent to include in the claim scope the use of allelic, interspecies, or man-made variants that have an amino acid sequence at least 90% identical to SEQ ID NO:17 and retain the same functionality. Percent sequence identity of a polypeptide to a reference amino acid sequence is a structural property of the polypeptide, because such percent identity relies entirely upon the amino acid sequence of this polypeptide. Moreover, the recitation of an amino acid sequence

identity of a polypeptide makes identification of the claimed polypeptide easily accomplished by one of skill in the art. Algorithms for determining percent sequence identity and sequence similarity for the identification of amino acid sequences are well known to those of skill in molecular biology and are referred to in the present specification, for example, on page 21, line 28, to page 24, line 9. The present claims can be analogized with *Fiers*, *Lilly*, and *Enzo* in that they all relate to genetic material. The description of the claimed polypeptide monomers relies on a percent sequence identity to a reference sequence and thus establishes a structural feature in a manner even more direct than that in the *Enzo* case.

The claimed polypeptide monomers are also defined by shared functional features, *i.e.*, they are capable of forming a heteromeric voltage-gated potassium channel with at least one additional Kv alpha subunit. Besides methodologies well known to the ordinarily skilled artisan, the specification provides functional assays for identifying the polypeptides with such functional characteristics. On page 45, line 3, to page 47, line 19, and on page 63, line 25, to page 64, line 4, for instance, the specification discusses various means for testing the ability of a polypeptide monomer to form a heterologous voltage-gated potassium channel with another Kv alpha subunit. These assays and others known in the art thus allow one skilled in the art to identify the polypeptide monomers within the scope of the claims.

Thus, both structural and functional features commonly shared by all members of the claimed genus of polypeptides have been described in detail, which "clearly allow persons of ordinary skill in the art to recognize that [the applicant] invented what is claimed." *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). This description of the claimed invention is consistent with the holdings of *Lilly*, *Enzo*, and *Amgen*.

3. The Structural and Functional Features Are Well Studied and Readily Testable

Applicants in addition wish to emphasize that the claimed subject matter of this invention relates to a special class of polypeptides: subunits of a voltage-gated potassium (Kv) channel, which have been extensively studied and characterized. As discussed in the previous sections, there exists in the art an abundance of detailed knowledge of voltage-gated potassium channels and their subunits. Besides the human Kv6.2 (whose amino acid sequence is set forth

in SEQ ID NO:17), the specification also discloses a mouse ortholog (whose amino acid sequence set forth in SEQ ID NO:1). The detailed knowledge includes specific structural features of Kv channel subunits, for instance the "subunit association" region and the conserved S4-S6 region (see, *e.g.*, page 10, lines 3-10, of the specification). A sequence alignment between SEQ ID NO:1 and SEQ ID NO:17 (attached as Exhibit A) further reveals regions within the proteins that are conserved among the interspecies orthologs. A person of skill in the art would be able to, upon reading the present application and with the aid of sequence alignment tools, compare the similarity among SEQ ID NO:17 and other Kv channel monomer sequences (particularly the amino acid sequence of mouse Kv6.2 as shown in SEQID NO:1) to determine which amino acid residues are commonly conserved through evolution, which other residues are not conserved, and which ones are tolerant to conservative substitutions. Thus, the artisan would be able to, with a reasonable level of certainty, predict or envision alternative amino acids at certain residues in functional variants derived from SEQ ID NO:17 with at least 90% sequence identity to SEQ ID NO:17.

Because of this specific knowledge and the technologically advanced state of the art, the present disclosure allows an ordinarily skilled artisan to readily produce variants of the exemplary polypeptide monomer (which has the amino acid sequence of SEQ ID NO:17) that are likely to retain the biological activity as a subunit of a heterologous voltage-gated potassium channel when complexing with another Kv alpha subunit. On the other hand, the functionality of these variants is readily verified by methods well known in the art or taught in the specification. Given the description of the exemplary Kv6.2 polypeptide monomer and the well defined, readily verifiable nature of both structural and functional features commonly shared by the claimed genus of polypeptide monomers, Applicants contend that a sufficiently detailed description of the claimed invention has been provided, such that "one skilled in the art can reasonably convinced that the inventor had possession of the claimed invention." MPEP §2163 I.

As such, Applicants contend that the specification does provide a sufficiently detailed description of the claimed invention to show the inventors' possession of the invention. The withdrawal of the written description rejection is therefore respectfully requested.

Enablement

Claims 11-15 were also rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. Specifically, the Examiner alleged that the specification fails to provide proper enablement for all polypeptide monomers within the claim scope. Applicants respectfully traverse the rejection, particularly in view of the present amendment.

1. Standard for Enablement

According to the MPEP, to satisfy the enablement requirement, the information contained in a patent specification must be sufficient to inform one skilled in the relevant art how to both make and use the claimed invention. MPEP §2164. Whether the enablement requirement is met depends on whether undue experimentation is necessary for one of skill in the art to practice the invention in light of the disclosure. MPEP §2164.01.

As set forth by the Federal Circuit in *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), multiple factors should be considered when determining whether any necessary experimentation is undue. These factors include:

(a) the breadth of the claims;
(b) the nature of the invention;
(c) the state of the prior art;
(d) the level of one of ordinary skill;
(e) the level of predictability in the art;
(f) the amount of direction provided by the inventor;
(g) the existence of working examples; and
(h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Furthermore, to reject a claim for lack of enablement, the Examiner must carry the initial burden to establish a reasonable basis for questioning the enablement provided by the specification. MPEP §2164.04.

2. No Undue Experimentation Is Necessary to Practice the Claimed Invention

As far as the breadth of the claims is concerned, the amended claims are drawn to a polypeptide monomer comprising an alpha subunit of a heteromeric potassium channel. The polypeptide monomer forms a heterologous Kv channel with at least another alpha subunit of Kv alpha subunit and has at least 90% sequence identity to SEQ ID NO:17. It is Applicants' intent to include in the claim scope the allelic, interspecies, or man-made variants of SEQ ID NO:17, so long as the variants have a certain level of sequence homology (*e.g.*, 90% or greater) to SEQ ID NO:17 and retain the ability to form a heterologous voltage-gate potassium channel with another Kv alpha subunit.

The claimed polypeptide monomers are defined by shared functional features (*i.e.*, forming a voltage-gated potassium channel with another Kv alpha subunit) and structural features (*i.e.*, having at least 90% sequence identity to SEQ ID NO:17). Because a person of ordinary skill in field of molecular biology can easily determine the terms used to define the functional and structural features, the claim scope is set forth clearly and the claims are thus not overly broad or vague.

As far as the nature of the invention is concerned, this invention resides in the discovery of a subunit of a novel Kv6.2 voltage-gated potassium channel. As stated above, the claimed polypeptides are defined by the shared functional and structural characteristics, which can be routinely tested and determined by employing standard techniques in the relevant research field.

As far as the state of the prior art is concerned, there should be no dispute that prior to the present invention, there already existed a significant amount of knowledge related to voltage-gated potassium channels and their subunits. In particular, a number of other Kv channel

subunits from various species (*e.g.*, human Kv2.1) had been identified and characterized. Thus, the prior art is in a highly advanced state.

As far as the level of one of ordinary skill in the art is concerned, the relevant research field of the present invention is molecular biology, where the substantive knowledge was abundant and the techniques for conducting these types of studies were well established, highly sophisticated, yet routinely practiced by the artisans. In short, the ordinary level of technical skill in the relevant art was high.

As far as the level of predictability in the art is concerned, such predictability refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. What is known in the art provides evidence as to the question of predictability. MPEP §2164.03. In the present case, the basic techniques in the art of molecular biology, such as techniques for cloning/subcloning, transfection, recombinant expression of proteins, and nucleic acid-protein binding, have been in existence for over two decades and have since improved dramatically to reach a high level of technical sophistication and predictability. As an example, the book *Molecular Cloning* had presented its third edition in 2001. In addition, as discussed above, much is known about the structural and functional features of other voltage-gated potassium channels. Therefore, a significant level of predictability exists in the relevant art.

Concerning the amount of direction provided by the inventor, the present application provides ample direction for an artisan to practice the claimed invention. For example, the application provides cloning methods for isolating the polynucleotide sequences encoding a Kv alpha subunit (page 28, line 21, to page 31, line 29, and page 62, line 1, to page 63, line 24); the application also teaches methods for recombinantly expressing the polypeptide (page 32, line 1, to page 34, line 11); the application further describes methods for purifying the recombinantly produced polypeptide (page 34, lines 14, to page 37, line 14); the application in addition offers assays for analyzing the functional characteristics of the claimed polypeptide in forming a heterlogous voltage-gated potassium channel (page 63, line 26, to page 64, line 4). As

such, a large amount of detailed direction is given in the present disclosure for practicing the claimed invention.

As far as working example is concerned, the present application provides one working example of the functional Kv6.2 monomer: SEQ ID NO:17, which favors a finding of adequate enablement.

Concerning the quantity of experimentation needed to make or use the invention, it is not disputed that some experimentation may be necessary to practice the present invention as defined by the pending claims. Yet "the test [of undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 190 USPQ 214, 217-19, (CCPA 1976)).

MPEP §2164.01 notes that, complex experimentation is not necessarily undue, if the art typically engages in such experimentation. The pending claims now define the claimed polypeptide monomer as having an amino acid sequence at least 90% identical to SEQ ID NO:17. Sequence alignment between two or more Kv alpha subunit sequences (such as the one shown in Exhibit A) provides highly valuable indication to a skilled artisan which amino acid residues are likely to tolerate modification and which others are unlikely to tolerate modification, such that the artisan would not randomly mutate amino acid residues in hope of obtaining a functional variant; instead, the process of generating functional variants of SEQ ID NO:17 would be performed in a focused and guided manner, resulting in a relatively small number of variants, which have a relatively high probability of retaining the desired functionality.

Because any necessary experimentation for practicing the claimed invention in the instant case would be routine for an ordinarily skilled artisan who is familiar with the well established techniques of molecular biology and biochemistry, involving standard techniques such as mutagenesis, subcloning, recombinant protein expression, DNA-protein binding assays, which have been constantly employed and improved by researchers in the relevant field over the last twenty years or so, such experimentation does not constitute undue experimentation.

In summary, Applicants do not believe that the *Wands* factors, when considered as a whole, support the finding of necessary undue experimentation. Accordingly, Applicants respectfully submit that the enablement rejection under 35 U.S.C. §112 should be withdrawn.

C. 35 U.S.C. §102

Claims 12-14 were rejected under 35 U.S.C. §102(b) for alleged anticipation by Su *et al.* Applicants respectfully traverse the rejection.

To anticipate a pending claim, a prior art reference must provide, either expressly or inherently, each and every limitation of the pending claim. MPEP§2131. According to the Examiner, Su *et al.* describe an amino acid sequence that has 53.7% overall sequence identity to SEQ ID NO:17 of this application. See, *e.g.*, page 11 of the Office Action mailed January 12, 1007. In contrast, the amended independent claim 11 recites that the claimed polypeptide monomer has an amino acid sequence with greater than 90% sequence identity to SEQ ID NO:17. The Su reference does not provide this claim limitation and therefore cannot anticipate the pending claims. The withdrawal of the anticipation rejection is respectfully requested.

D. 35 U.S.C. §103

Claims 11-15 were further rejected under 35 U.S.C. §103(a) for alleged obviousness over Su *et al.* in view of Jacobs *et al.* Applicants respectfully traverse the rejection.

In order to establish a *prima facie* showing of obviousness, three requirements must be satisfied: all limitations of a pending claim must be expressly or impliedly disclosed by prior art references; there must be a suggestion or motivation in the art for one skilled artisan to combine the limitations; and there must be a reasonable expectation of success in making such a combination. MPEP §2143. As discussed above, the Su reference fails to provide at least one limitation of the pending claims: a polypeptide monomer having an amino acid sequence at least 90% identical to SEQ ID NO:17. On the other hand, the Jacobs reference was cited for the purpose of providing the limitation relating to the generation of polyclonal antibodies against a protein; it too fails to provide the missing limitation. As such, the two references fail to provide

all limitations of the pending claims of this application and no *prima facie* obviousness has been established. The withdrawal of the obviousness rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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Attachment (Exhibit A: sequence alignment between SEQ ID NOs:1 and 17)
CG:cg
60991022 v1